

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

R E M A R K S

Upon entry of the above amendment, claims 13-27 will be pending in the present application.

Compliance with 37 C.F.R. §1.821-§1.825

Applicants submit the following in order to comply with the Requirements for Patent Applications containing Nucleotide Sequences and/or Amino Acid disclosures for the above-identified application:

(a) a computer readable form copy of the "Sequence Listing";
and

(b) a paper copy of the "Sequence Listing".

The content of the paper copy and the computer readable form are the same, and where applicable include no new matter, as required by 37 C.F.R. §1.821(e)-§1.821(g) or §1.825(b) or §1.825(d).

In view of the above, Applicants submit that they have complied with the requirements under 37 C.F.R. §1.821-1.825.

New Oath or Declaration

A new Declaration in compliance with 37 CFR §1.67 (a) is attached.

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

The Present Invention

The presently claimed invention is directed toward the preparation of modified self-proteins and immunogenic compositions which contain these self-proteins which are capable of inducing a high-titered and rapid antibody response against the self-proteins in a heterogeneous MHC-population, so that autovaccines against said proteins can be prepared. Such modified self-proteins also provide a useful tool in the preparation of antibodies, both monoclonal and polyclonal, using known techniques.

The present invention is based on the surprising finding that substitution, by molecular biological means, of one or more peptide fragments in the self-protein by a corresponding number of immunodominant foreign T-cell epitopes in such a way that the tertiary structure of the self-protein is essentially preserved renders this self-protein analog highly immunogenic leading to a profound antibody response against the unmodified self-protein. By substituting the epitopes into the self-protein the immune response elicited is furthermore not only restricted to the known MHC class II type of the inserted immunodominant T-cell epitope but surprisingly, the modified self-protein also elicits an autoantibody response in other MHC-haplotypes. Consequently, the

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

recombinant self-protein analogs will be self-immunogenic in a large population expressing many different MHC class II molecules.

The method of the invention has a number of surprising and beneficial effects compared to the known techniques for induction of autoantibody responses. These include:

- a more rapid and high-titer autoantibody response is raised compared to the conventional hapten/carrier technology where the self-antigen is chemically coupled to a foreign carrier antigen
- no undesired and potentially allergic reaction towards foreign carrier antigens can be elicited
- different from chemical conjugates in general, the modified self-protein analogs according to the present invention are chemically and pharmaceutically well-defined
- the preserved tertiary structure of the modified self-protein analogs according to the present invention enables an optimal induction of the autoantibodies recognizing the native self-protein

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

- the modified self-protein analogs according to the present invention are immunogenic in a heterogeneous MHC population
- the fine specificity of the induced autoantibodies can be regulated by insertion of the T-cell epitope in appropriate positions inside the self-protein
- toxic self-proteins, such as, e.g., $\text{TNF}\alpha$, can be detoxified if the T-cell epitope is inserted at an appropriate position in $\text{TNF}\alpha$. Non-modified $\text{TNF}\alpha$ -molecules conjugated or fused to a foreign carrier antigen could potentially be toxic
- by insertion of known immunodominant T-cell epitopes towards which humans frequently are immune (e.g., epitopes derived from tetanus toxoid) it is possible to test the immunogenicity of said modified self-protein analogs *in vitro* without the need for prior immunization of humans.

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

35 U.S.C.S 112, Second Paragraph

The claims presented are definite and particularly point out and distinctly claim subject matter which Applicants regard as the invention.

With respect to the use of the term "providing a self-protein by molecular biological means", this has now been amended to --substituting, by molecular biological means, one or more peptide fragments of the self-protein by a corresponding number of peptides each containing at least one immunodominant T-cell epitope which is foreign to the animal species--. The term would be clear to a person of skill in the art to which the invention pertains. Clearly the Examiner even knows and understands what this term means and has referred to the construct of the Löwenadler et al., cited reference as being made by molecular biologic means. The Examiner is referred to page 5, lines 4-5 of the Office Action dated April 21, 1997.

With respect to the use of the term "preserving flanking regions", this has been retained in the claims (see new claim 14) "Flanking regions" refers to the regions originating from the original unmodified self-protein present on each side of the peptide containing the T-cell epitope.

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

35 U.S.C. § 112, First Paragraph

With respect to any previous rejection of the claims for being non-enabled, it is the Examiner's position that the specification does not disclose how to use the claimed method or autovaccine for the treatment of disease in vivo in humans. According to the Examiner, the claimed autovaccines read on autovaccines of the treatment of human disease (emphasis added). It is respectfully submitted that the Examiner has not appreciated what Applicants regard as their invention and which diseases are involved.

The invention is related to self-proteins, i.e., proteins which are present in the human or animal organism. As explained on page 2 the presence of some self-proteins is inexpedient in situations where they, in elevated level, induce disease symptoms. As examples are mentioned high levels of IgE, which might induce type I allergy and TNF α , which might induce cachexia in some patients or influence on the inflammatory process.

The present invention aims at removing or down-regulating self-proteins so as to reduce their potential of causing diseases or symptoms or signs of disease. Such self-proteins are removed by circulating autoantibodies raised against the modified self-proteins produced according to the present invention. The modified

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

self-protein in turn are administered in the form of vaccines wherein the modified self-proteins are essential active ingredients.

As further elaborated on page 5, lines 27-30, the problem to be solved is to provide immunogenic compositions which are capable of inducing a high-titered and rapid antibody response in a heterogeneous MHC-population against pathogenic self-proteins, so that vaccines against said proteins can be prepared. So, in essence, the method claims previously considered by the Examiner do not represent a "method of treatment of diseases in human (or animals)" in its usual sense. In particular, it is not a method of the type claimed in the cited *Aggarwal* decision, viz., a method for treatment of any tumor (in any animal species) by administering an effective amount of human lymphotoxin. Claim 13 of the present invention is a method for producing a modified self-protein not a therapeutic method. Therefore, the citation of *Aggarwal*, and *Osband* for that matter, are not relevant to this claim.

The invention is specifically limited to the modification of a given self-protein in order to raise antibodies against the very same protein whereby it can be removed or down-regulated following

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

administration of said modified self-protein also denominated "self-protein analog".

Applicants do not claim that the fact that a murine self-protein analog raised antibodies against the murine self-protein as shown in the examples is evidence that a corresponding human self-protein analog would also raise antibodies against the murine self-protein (although it might well be so).

Likewise we are not facing a problem similar to that described by Osband, viz., that Applicants have presented data showing that a human self-protein analog raises antibodies against the corresponding murine self-protein (although it might well be so depending on the sequence homology) and claims this to be evidence that the human self-protein analog would also raise antibodies against the corresponding human self-protein. Osband's paper is focused on cancer immunotherapy, primarily therapy against tumors.

The very word "self-protein" clearly indicates that Applicants are dealing with homologous species, so that it is reasonable to assume that positive murine data for a given murine self-protein is evidence of expected positive human data for the corresponding human self-protein as regards the ability to raise antibodies.

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

"Many immunotherapeutic agents are inactive in other species" says Osband, page 103, line 4 from the bottom and goes on "[I]n addition to the extreme complexity of the host-tumor immunorelationship, animal models do not fully mimic the biology of human patients with cancer. Finally, the immune system is obviously different in humans and animals, and it is not surprising that immunotherapeutic agents fail to demonstrate comparable activity in animals and humans. For all these reasons it will be necessary to develop immunotherapy intended for humans in humans". This is exactly what Applicants have done.

Applicants do not claim to have developed a miracle cure against cancer in humans, substantiated by tests in a few mice. Applicants have focused on a particular immunological problem, viz., an overproduction of autoproteins which might induce various diseases, among which are various forms of cancer.

Applicants' self-protein analogs induce antibodies against the original self-protein. If this self-protein is known to induce a particular form of cancer and is removed or down-regulated in time, chances are that the patient will not develop cancer. This is the whole rationale behind the use of vaccines. Unless the incubation

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

time is very long, such as for rabies, vaccines are used as preventive measure.

However, it is tempting to speculate that the growth of a given tumor or the proliferation of a given form of cancer cells induced by a particular self-protein is dependent on a constant delivery of said self-protein and if this is so, that a regular administration of a self-protein analog according to the present invention might deprive the cancer cells from an essential element and stop the cell proliferation. Whether or not this is the case with one or more of the analogs produced according to the present invention remains to be seen.

The Examiner cites *ex parte Aggarwal*. However, the reasons 1-3 stated in the Examiner's argumentation are not at all relevant for the presently claimed invention. First of all, as presently drafted, independent claim 13 includes a confirmation that the modified self-protein is capable of inducing an antibody response against the unmodified self-protein. This must inherently mean that the protein administered is effective!

As for the 3 reasons stated by the Examiner, the following arguments apply for each reason, respectively:

1. Since the present invention aims at introducing only minor changes (substitution with, e.g., 1 single foreign T-cell epitope in the entire self-protein) in order to render a normally non-immunogenic protein immunogenic, immunological inactivation of the modified self-protein is in fact desired, since this will mean that the modified protein is immunogenic. As for proteolytic degradation, this is also desired in order to obtain a processed T-cell epitope to be presented by an antigen-presenting cell (see page 1, lines 19-27 of the specification).
2. Since the "target area" is the immune system, a simple injection of the modified self-protein antigen into the bloodstream or subcutaneously will ensure that it engages the cells of the immune system. In the present case there are thus no problems in reaching the target area.
3. Since the modified self-protein has a very high degree of homology with the unmodified self-protein and has a tertiary structure which is substantially the same as that of the unmodified self-protein, it must be reasonably expected that the modified self-protein does

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

not introduce side-effects which go beyond those of the unmodified protein; in fact, the introduction of the foreign T-cell epitope can be made so as to render the modified protein less toxic than the unmodified self-protein, see page 9, 1st full paragraph in the specification. It should also be borne in mind that the severity of side-effects always has to be balanced against the severity of the disease to be treated. In the case of cancer, it is well-known that the toxic side-effects has to be tolerated because of the fatal outcome of the disease. At any rate, the toxicity issue can only be determined on a case-by-case basis, and it should be remembered that the present invention is not limited to the modification of one single self-protein. It does not seem to be reasonable by the Examiner to require documentation that each and every possible modified self-protein is non-toxic.

The Examiner also cites *Osband* in support of the viewpoint that murine data does not enable the use of the inventive method in a human system.

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

First of all, the present invention is in no way restricted to human use. Vaccines against self-proteins in animals are also contemplated. In fact, Applicants' invention has been successfully applied in other animal models than the murine model.

Second, the present invention is not directed to an immunotherapy which should first be tested in mice and thereafter applied in humans. Rather, the present invention focuses on a method of rendering self-proteins (which are normally not antigenic in their natural environment) antigenic. The invention has demonstrated that two proteins (ubiquitin and TNF- α) which are normally not antigenic in mice can be rendered antigenic, i.e., it is possible to force the mice to produce antibodies reactive with the two proteins when immunizing the mice with self-proteins modified according to the invention. And, even though it is true that there are differences between the immune systems in man and in the mouse, the similarities are greater than the differences. In this connection, it should be noted that experiments have been performed on TNF- α and ubiquitin and both of these attempts were successful. This is in our opinion a very strong indication that the method of the invention is generally applicable, since the chances of getting two "lucky strikes" as the first results would

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

be close to zero if the invention was of limited use and applicability.

All things considered, the list of problems in the paragraph bridging pages 3 and 4 with regard to *Ex parte Aggarwal* might have been relevant in their context in view of Aggarwal's claims directed to a method for the treatment of (any) tumors (in any species) by means of lymphotoxin. However, it is respectfully submitted that they are not pertinent to the present invention.

The rejection under 35 U.S.C. 112, first paragraph concludes with a statement as to:

- 1) lacking disclosure of an actual autovaccine suitable for the treatment of human diseases or guidance as to how such an autovaccine should be made, in particular a human TNF- α autovaccine,
- 2) lacking guidance as to where T-cell epitopes could be inserted in human TNF- α (an by inference presumably in any self-proteins) without disrupting the overall tertiary structure,
- 3) lacking guidance as to what dosage to administer,

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

which taken together leads the Examiner to the fact that undue experimentation is required in order to practice the invention citing ex parte Forman.

The applicant acknowledges that the "undue experimentation" proscription is well established in the U.S.

However, as amply put in ex parte Forman, page 542, right column (citations omitted, emphasis added):

"The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art...The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed."

In order to rebut the "undue experimentation" objection, applicants have consulted Professor Sven Frøkjaer of the Royal Danish School of Pharmacy, who is a person skilled in the art of

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

protein and peptide formulation, and his declaration (hereinafter the Frøkjaer declaration) is enclosed with the present amendment.

Turning to the individual objections cited above, it is apparent from the Frøkjaer declaration, sections 7 and 8 that the formulation of a vaccine based on purified proteins such as the modified self-proteins of the present invention, including selection of suitable adjuvants is routine to a person skilled in the art. The person skilled in the art will readily acknowledge that a suitable amount of peptide in a peptide vaccine will be from 1 - 1000 μ g, typically 10 - 100 μ g, depending on the actual peptide and the vaccine formulation.

Apart from this general statement, the specification is far from being without guidance in these respects. The Examiner's attention is directed to the paragraph bridging pages 10 and 11, the "mouse vaccine" described on page 12, lines 1-2, where the person skilled in the art would as a matter of routine substitute Freund's complete adjuvant with a suitable adjuvant for human purposes.

As for the guidance with regard to the conservation of the tertiary structure Professor Frøkjaer in section 5 recites a number of routine screening procedures available to the person skilled in

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

the art and concludes in section 6 that such screening for changes is a straightforward procedure in the development of protein-based drugs. In other words, a person of skill in the art would know how to set up a simple screening system for identifying modified self-proteins having the preserved tertiary structure.

Finally, with regard to what dosage of any particular agent needs to be administered, this is a case for the physician in charge of the patient, not for the patent Examiner. As stated by Frøkjaer, section 9, the amount of active ingredient is optimized by routine experimentation.

The specification contains detailed information of the doses used in the experiments with mice, and based on these data it might be possible to extrapolate to reasonable human dosages.

It can be said with quite some certainty that the immunogenic effective amount of a polypeptide does in principle not vary extensively between humans, small rodents, such as, e.g., mice, and large mammals, such as elephants. In other words, the immune response is not concentration dependent. Presumably, the explanation is that the polypeptide antigen following injection is upconcentrated in the lymph nodes, where interactions between B- and T-cells take place, and where antigen presenting cells, such

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

as, e.g., macrophages, can activate the T_H -cells necessary for the immune response. This "unconcentration" of polypeptide antigens in the lymph nodes takes place in all mammals (and with essentially the same efficiency). The immune response to a polypeptide antigen is thus apparently dependent on a "principle of closeness" and on activation of a certain minimum of cells, and due to the function of the lymph nodes as a filter, this entails that essentially the same amount of protein is required in order to immunize a mouse and an elephant. Thus, it is easy to extrapolate from animal test results to humans; it is not necessary to make calculations on body weight and volume of distribution, as is the case with real drugs which are concentration dependent.

However, each patient suffering from an undesirably high level of self-proteins must be evaluated individually and the dosage of immunogenic agent comprising the modified self-protein will have to be adjusted and possibly readjusted in accordance with the severity of the disease induced by the increased level and the speed with which the effect of the formed antibodies proceed.

Generally speaking, the immunogenic composition will be administered in a manner compatible with the dosage formulation (Frøkjær, section 9) and in such an amount as will be

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

therapeutically effective and immunogenic. The quantity to be administered depends on the subject to be treated, including, e.g., the capacity of the individual's immune system to mount an immune response, and the degree of protection desired which in turn depends on the level of undesired self-protein in the patient. Suitable regimens for initial administration and booster shots are also variable, but are typified by an initial administration followed by subsequent inoculations or other administrations.

As is apparent from the Frøkjaer declaration, the manner of application may be varied widely. Any of the conventional methods for administration of a protein-based vaccine are applicable. These are believed to include oral application, parentally, by injection on the route of administration and will vary according to the age of the person to be vaccinated and, to a lesser degree, the size of the person to be vaccinated.

Some of the modified self-proteins according to the present invention are sufficiently immunogenic in a vaccine, but for some of the others the immune response will be enhanced, if the vaccine further comprises an adjuvant substance (Frøkjaer, section 8).

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

35 U.S.C. § 103(a)

The Examiner has previously cited Löwenadler et al. in view of Berzofsky et al., Hellman and Etlinger.

Applicants submit that the present invention is neither taught nor suggested by the art cited. A brief discussion of the cited art follows:

Löwenadler refers to the use of a T-cell epitope ovalbumin 323-339 (Ova) in order to include antibody response towards foreign proteins. This well-known T-cell epitope is also used by the present Applicants in two examples of modified self-proteins used in the murine vaccination experiments, when raising antibodies against the self-proteins; murine TNF α and ubiquitin.

In Löwenadler however, antibodies are raised in mice against a fusion protein containing two foreign proteins, viz. the enterotoxin from *E. coli* and the C-terminal nonapeptide part of human insulin like growth factor (IGF-1). Furthermore, the fusion protein is supplied with an IgG binding peptide from protein A. One or more copies of the Ova T-cell epitopes are attached as a fusion partner to the chimera of these foreign proteins, and are not inserted into any of the proteins but fused either to the C-terminal end, or between the two foreign fusion partners. Thus,

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

the Ova T-cell epitopes do not substitute any part of the enterotoxin or IGF-1 proteins, so as to essentially preserve their tertiary structure.

Notwithstanding the fact that Applicants also use the ovalbumin T-cell epitope, quite different experimental strategies are used, and entirely different considerations have been made in the design and execution of the method of the present invention. Applicants describe a method for raising auto antibodies against self-proteins. Applicants do not rely on fusion proteins but insert known immunodominant T-cell epitopes into the complete self-protein analogs. In particular, Applicants carefully substitute parts of the self-protein with T-cell epitopes of equal size so as to essentially preserve the size and tertiary structure in the formed self-protein analogs. In Löwenadler on the other hand, the original sequence of the fusion antigen (StaZZC) modified is only modified by insertion, there is not removal of part of the self-protein amino acid sequence and subsequent substitution with foreign T-cell epitope. In short, apart from Löwenadler neither teaching or suggesting modification of self-protein, Löwenadler merely discloses insertion of T-cell epitopes between different

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

fusion partners in a fusion protein with a view to investigating the effect on antibody production.

Berzofsky presents a review dealing with the nature of antigenic determinants recognized by antibodies. Amongst other well known facts, the review teaches that most antibodies against intact proteins bind conformational epitopes determined by the three-dimensional structure induced by the tertiary structure of the protein. However, since Löwenadler et al. teaches that a T-cell epitope should be inserted between fusion partners in a chimeric protein, the combination of Löwenadler and Berzofsky, in the event they would be combined, would be a fusion protein where the tertiary structure of each of the fusion partners sought is retained and where T-cell epitopes are inserted between the fusion partners. This construct is however, already the subject of Löwenadler et al.

Hellman teaches the breaking of the autotolerance towards a polypeptide part of a self-protein. The self-polypeptide is chemically coupled to a carrier protein, although it is also suggested to use molecular biological means. A purification "tag" is suggested as the carrier for the ease of purification. In this document no considerations are made regarding the importance of

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

inserting strong well-defined immunodominant T-cell epitopes. Single amino acid mutations in the autologous polypeptide are considered and it is speculated that new T-cell epitopes by chance could emerge from such mutations. In this document a polypeptide fragment, the constant CH₂-CH₃ domains of the much larger IgE protein, are used for raising the autoantibodies and some foreign carrier protein is coupled to this.

Thus, no considerations are made regarding the importance of essentially preserving the tertiary structure, let alone using the complete protein for facilitating the broadest possible range of autoantibody responses, or removing immunodominant self-epitope sequences. Furthermore, the induction of auto-antibodies by coupling of the autoantigen to a large carrier protein is not as efficient as the method according to the present invention. By inserting known immunodominant T-cell epitopes derived from, e.g., tetanus toxoid, as suggested in the present invention, an additional important technical advantage is obtained, namely the ability to test *in vitro* whether the inserted epitopes are correctly processed by the antigen presenting cells and subsequently presented to human tetanus toxoid specific T-cells. This makes it possible to test the immunogenicity of the self-

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

protein analogs without prior immunization of humans with these constructs.

Etlinger teaches the use of T-cell epitopes derived from tetanus toxoid as conjugate (or fusion) partners to poorly immunogenic antigens in order to obtain an enhanced immune response taking advantage of prior vaccines against tetanus. Again, the strategy suggested is conjugation which, as already discussed above in comments on Löwenadler et al, is different from the technique of substitution in accordance with the present invention. Specifically, Etlinger teaches conjugating a known immunodominant peptide sequence derived from *Plasmodium falciparum*, having the sequence NANP, to either tetanus toxoid (TT) or amino acid residues 73-79 of tetanus toxoid (TT73-79). These constructs can hardly be said to maintain the overall tertiary structure of the protein from which NANP is derived. They only teach that using TT73-79 as a fusion partner to a poorly immunogenic antigen or hapten will enhance the immune response against the poorly immunogenic antigen or hapten. Clearly, it does not suggest the use of TT73-79 as a **substituting** amino acid sequence within a self protein so as to substantially maintain the tertiary structure of the self-protein.

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

Response to the Examiner's Rejection of the Claims:

The Examiner has cited Löwenadler because it teaches that "a T helper cell epitope of 16 amino acids can be inserted into a chimeric protein and induce an autoantibody response (see Abstract)" and that "the T helper cell epitope is inserted in a location that would be expected to preserve the tertiary structure of the chimeric protein (see Figure 1)". However, as seen from the discussion of the art above, it is clear that Löwenadler differs from the present invention in that **substitution** of a self-proteins amino acid sequence does not take place and furthermore, Löwenadler does not teach **modification** of the self protein in accordance with the present invention. None of the other references cited by the Examiner teach or suggest either of these features of the presently claimed invention.

As the Examiner will be aware, in order to make out a *prima facie* case of non-obviousness the prior art must teach or suggest all the claimed limitations. Since the cited art fails to teach **substitution** of T cell epitopes and **modification** of the self-protein, in accordance with the presently claimed invention, and the Examiner has not addressed these differences, a *prima facie* case has not been made out.

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

Furthermore, for there to be a *prima facie* case, there must be a reasonable expectation of success. In view of the Examiner's rejection under 35 U.S.C. §112, first paragraph, it would seem that the Examiner does not consider that there would be such a reasonable expectation.

The Examiner has said that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Löwenadler et al. teach that by inserting T helper cell epitopes into a chimeric protein that increased antibody responses against difference types of epitopes of the protein can be obtained". However, it must be recognized that Löwenadler et al. is not concerned with the issue of raising antibodies against the self-proteins. A person of skill in the art, based on the teachings of Löwenadler, would not be motivated to induce the production of autoantibodies. The constructs of Löwenadler et al are foreign to any organism for the simple reason that they are chimeric. Hence, all that would be taken from Löwenadler et al. is that the immune response against a *foreign* fusion protein can be enhanced by insertion of T-cell epitopes between the fusion partners of such a foreign fusion protein. This clearly fails to teach or suggest the concept of

Serial No.: 08/955,373
Atty. Docket No.: 162/P58774US3

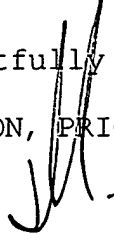
inducing an immune response against an antigen which is not in itself immunogenic because it is a self-protein in accordance with the present invention.

Applicants submit that, for the above reasons, there would be no motivation to combine the references cited by the Examiner, and even if it is shown that there would be, none of the references, either alone or in combination, teach or suggest the claimed invention. Favorable consideration of the application in view of the above amendments and submissions is respectfully requested.

Should the Examiner have any questions or comments, the Examiner is cordially invited to telephone the undersigned attorney.

Respectfully submitted,

JACOBSON, PRICE, HOLMAN & STERN, PLLC



D. Douglas Price
Registration No. 24,514

400 Seventh Street, N. W.
Washington, D.C. 20004
Telephone: (202) 638-6666
Atty. Docket No.: 162/P58774US3
Date: August 19, 1998
Enclosures: (a) New Declaration
(b) Sequence Listing (paper and CRF forms)
(c) Declaration of Professor Frøkjaer

M:\TKEEBL\8-98\P58774.AMD